EXHIBIT 3

CITIZEN PETITION LETTER ("CPL")

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VIA FEDEX

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CITIZEN PETITION

This petition for administrative action is submitted on behalf of the undersigned Petitioner pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "Commissioner") halt two ongoing trials of the drug Simufilam (formerly PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending a thorough audit by the FDA of the matters described herein.

Cassava Sciences is a public company that is focused on developing therapies targeted at Alzheimer's Disease. Cassava is currently sponsoring clinical trials NCT04388254 and NCT04994483 for its proprietary drug Simufilam, which is claimed to represent a novel approach to Alzheimer's treatment. In its recent SEC filings and elsewhere, the company has publicly announced the successful completion of its End of Phase 2 meeting for Simufilam with the FDA, and stated that the company and the FDA are aligned on key elements of a Phase 3 clinical program. The company has stated that it expects to initiate its Phase 3 program with Simufilam in September 2021.

Information available to the petitioner, however, which is summarized below and detailed in the enclosed technical report, raises grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy. Petitioner is therefore requesting the FDA to halt the clinical studies pending a thorough audit of the publications and data relied on by Cassava in support of its claims.

I. ACTION REQUESTED

Petitioner is requesting that the FDA halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the IND application for Simulifam's use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease. Petitioner is further requesting that the FDA oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease. The ongoing clinical trials should be paused until the satisfactory completion of these investigations.

II. STATEMENT OF GROUNDS

Petitioner has enclosed with this Petition (and incorporates herein) a detailed technical report presenting multiple reasons to question the quality and integrity of the research supporting Cassava's claims about Simufilam's use for Alzheimer's Disease. In sum, that report explains:

(1) All of the foundational science supporting Cassava's claims about Simufilam's use for Alzheimer's Disease comes from a series of papers with two common co-authors (Dr. Hoau-Yan-Wang at City University of New York and Dr. Lindsay Burns of Cassava). The studies of Drs. Wang and Burns were used by Cassava to obtain NIH grants and to open an Investigational New Drug (IND) application to study Simufilam. They form the foundation for the current clinical trials of Simufilam.

(2) No other lab has confirmed Cassava's research connecting Filamin A to Alzheimer's Disease, nor has any other lab confirmed that Simufilam binds or modifies Filamin A or has effects in Alzheimer's Disease models.

(3) Close review of the data and analyses in the foundational research papers and Cassava's recent publications of clinical trial analyses presents three primary areas of concern:

   a. The underlying papers of Drs. Wang and Burns involve extensive use of Western blot analyses to support their claims connecting Simufilam to Alzheimer's. Detailed analysis of the western blots in the published journal articles shows a series of anomalies that are suggestive of systematic data manipulation and misrepresentation.

   b. Some of the foundational studies published by Drs. Wang and Burns make claims about Simufilam's effects in experiments conducted on postmortem human brain tissue. The methodology allegedly used in these experiments defies logic, and the data presented again have hallmarks of manipulation.

   c. Cassava's presentation of clinical biomarker data from the Phase 2b trials raises questions about the validity of the data. The CSF samples in this study were first analyzed by an outside lab, which found that Simufilam was ineffective in improving the primary biomarkers end point and high variability in other biomarkers. But Cassava had these samples analyzed again and this time reported that Simufilam rapidly and robustly improved a wide array of

biomarkers. Cassava has not fully published the data from this reanalysis, but a presentation poster that it published on July 26, 2021, which appears to describe aspects of that work, shows signs of data anomalies or manipulation.

(4) Six further aspects of the research by Drs. Wang and Burns are incompatible with scientific norms, and these claims raise further suspicions.
   a. Remarkably High Affinity Binding Between PTI-125 and Filamin A.
   b. Remarkably High Affinity Binding Between Naloxone and Filamin A.
   c. Isoelectric Focusing Experiments in Multiple Papers Indicate 100% of Filamin in Altered Conformation in Alzheimer's Disease and largely Restored to Correct Conformation by PTI-125.
   d. Novel Blood Diagnostic SavaDx Represents Plasma Filamin A Level
   e. PTI-125/Simufilam Improves Memory in a Mouse Model of Alzheimer's Disease.
   f. PTI-125/Simufilam Blocks the Interaction Between β-amyloid and α7- Nicotinic Acetylcholine Receptors.

Petitioner submits that the extensive evidence set forth in the enclosed report, which presents grave concerns about the quality and integrity of the scientific data supporting Cassava's claims for Simulifam's efficacy, provides compelling grounds for pausing the ongoing clinical trials until the FDA can conduct and complete a rigorous audit of Cassava's research.

III. ENVIRONMENTAL IMPACT

Petitioner states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

IV. ECONOMIC IMPACT

Economic impact information will be submitted at the request of the Commissioner.

V. CERTIFICATION

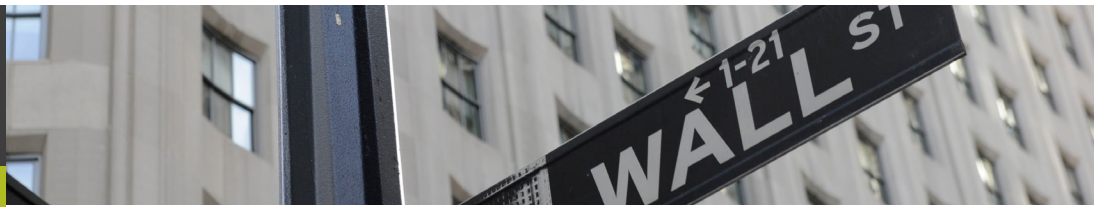
The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Jordan A. Thomas
Enclosures

CITIZEN PETITION REPORT ("CPR")

Labaton Sucharow



Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known As Simufilam

August 18, 2021

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A. Executive Summary

For over 15 years, Cassava Sciences (previously Pain Therapeutics, Inc, PTI) has funded the lab of Dr. Hoau-Yan Wang at City University of New York (CUNY). Together with Dr. Lindsay Burns at Cassava, Dr. Wang has published nearly a dozen papers connecting Filamin A protein with pain and Alzheimer's disease (AD).

Cassava Sciences created a drug candidate called simufilam (previously PTI-125) that they claim binds Filamin A and has beneficial effects in biochemical and animal models of AD. The studies from Drs. Wang and Burns discussed in this dossier were used by Cassava Sciences to garner NIH grants and to open an investigational new drug (IND) application to study simufilam in AD patients. They form the basic science foundation for two completed clinical trials (phase IIa and IIb) which exposed over 70 patients to simufilam. Cassava Sciences is currently recruiting 200 additional patients for a follow-up open-label trial.

This report raises concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate. To preface the analysis that follows, no other labs have confirmed this research connecting Filamin A to pain or AD. No other labs have confirmed that simufilam binds or modifies Filamin A or has effects in AD models.

In this document, three primary concerns are raised:

- The validity of clinical biomarker data: Biomarker analysis from patients treated with simufilam in Cassava's double-blind study forms a primary basis of Cassava's claim that simufilam engages its target in the central nervous system, but there are concerns about the integrity of this data. The CSF samples in this study were analyzed by an outside lab, which found that simufilam was ineffective in improving the primary biomarker end point and showed high variability in other biomarkers. However, Cassava Science had these samples bioanalyzed again and the data were finalized in

an academic lab, which apparently refers to Dr. Wang. This re-analysis showed that simufilam rapidly and robustly improved a wide array of CSF biomarkers. Whereas Cassava has not fully published this reanalysis, Cassava's 26 July 2021 poster presumably describing aspects of that work shows signs of data manipulation.

- The integrity of western blot analyses: Western blotting was extensively used by Drs. Wang and Burns over the past 15 years to support their foundational scientific claims and underscores their SavaDx clinical plasma biomarker. Detailed analysis of the western blots in the published journal articles from Drs. Wang and Burns shows a series of anomalies. The extent of these anomalies forms a 15-year pattern that strongly suggests systematic data manipulation and misrepresentation.
- The integrity of analyses involving human brain tissue: Simufilam is reported to bind to its target and modify a range of downstream molecules in experiments conducted on post-mortem human brain tissue from subjects with Alzheimer's disease and neurological controls. The same human brain specimens are used across the studies from 2008-2017, so the results are premised on human neurons remaining viable up to 13 hours after death, then being successfully reanimated after nearly 10 years in frozen archival without any advanced cryopreservative techniques. The complex, multi-step cellular processes the authors claim to observe in tissue that has been dead for a decade are contrary to a basic understanding of neurobiology. As with the western blot data, there are anomalies in the presentation of the data which again strongly suggest manipulation.

In the appendix, six additional areas of concern are raised. These frequent errors and anomalies occur in a pattern which is frequently favorable to the authors' hypotheses and is of

sufficient magnitude to strongly suggest scientific misconduct. This scientific work is foundational to the link between simufilam and its supposed target Filamin A in AD. Consequently, urgent action is advisable to limit patient exposure to this drug, until an appropriate investigation is completed.

Finally, we make six specific recommendations:

- The NIH and CUNY should audit the publications and lab of Dr. Wang to determine the existence and extent of data manipulation and possible fraud in all papers and grant applications from Drs. Wang and Burns.
- The FDA should audit both these publications and the IND application for simufilam's use in AD.
- The FDA should audit all clinical biomarker studies of simufilam in AD.
- The FDA should oversee 3rd party reanalysis of all clinical biomarker studies of simufilam in AD.
- The FDA should pause ongoing trials with simufilam pending these investigations.
- The academic journals which published the studies discussed herein should review and retract them to correct the public record, if the concerns remain after adequate investigation.

B. Background

This letter details a long-standing pattern of seemingly intentional data manipulation and misrepresentation in scientific papers and corporate disclosures authored primarily by Drs. Hoau-Yan Wang, Associate Medical Professor, City University of New York, and Lindsay A Burns, Sr. Vice President of Neuroscience at Cassava Sciences. All the information detailed herein was obtained from public, non-proprietary sources. These apparent falsifications have helped garner

>$5,000,000 in NIH grants for preclinical/clinical studies, attract >$250,000,000 in public fundraising by Cassava Sciences and misdirect therapeutic studies for patients suffering from Alzheimer's Disease (AD). In the interest of **the safety of patients with Alzheimer's disease enrolled in Cassava Sciences' ongoing clinical trials**, as well as the NIH and other stakeholders, the biomedical and financial communities must be made aware of these apparent falsehoods. The laboratory of Dr. Wang and Cassava Sciences warrant an audit to comprehensively evaluate the integrity of the scientific data.

For >15 years, Dr. Wang has collaborated with Cassava Sciences, formerly known as Pain Therapeutics Incorporated (PTI). Cassava Sciences is developing simufilam, a drug which was initially designated PTI-125, as a disease modifying treatment for Alzheimer's disease. Simufilam is claimed to bind to bind a cytoskeleton-associated protein called Filamin A and thereby benefit a range of Alzheimer's disease related neuropathologies. This line of research is unique to Dr. Wang and Cassava Sciences.

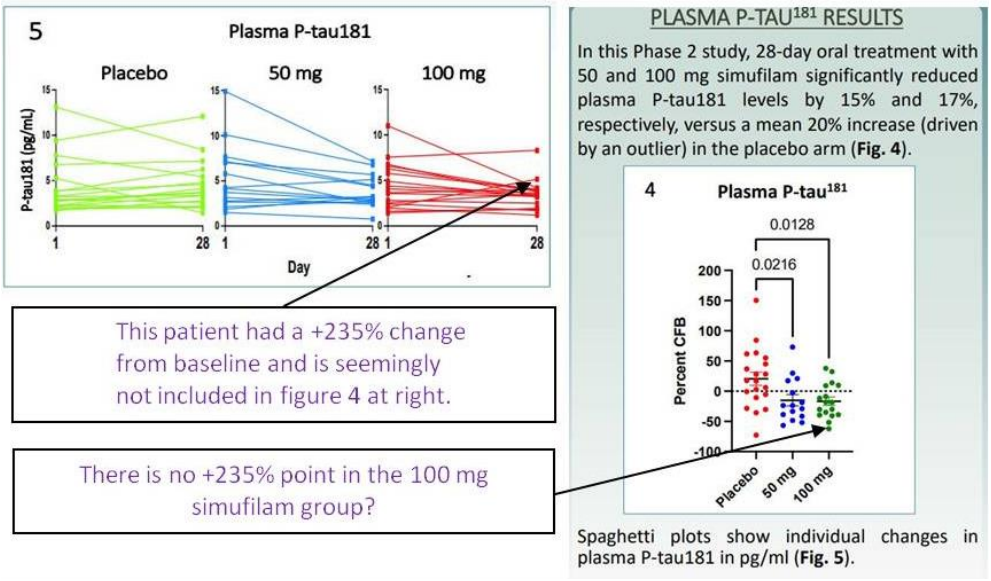
In reviewing this work, several results were encountered that are most unexpected and are probably unique to Drs. Wang, Burns and Cassava Sciences. Consequently, we investigated the published journal articles and other public sources of data underlying the development of simufilam in greater detail. This initial analysis suggests a pattern of clear errors and anomalies that are consistent with data manipulation and misrepresentation. These findings undercut the foundational science on which simufilam therapy is based.

C. Major Concerns

C.1. Concern #1: Integrity of Clinical Biomarker Data

NIH STTR grants (AG057329 & AG060878) funded Cassava Sciences' double-blind placebo-controlled phase II trial of PTI-125 (50, 100 mg QD) in 64 AD patients (NCT04079803). The primary end points reported were changes from baseline (day 1 to day 28) for a series of CSF

biomarkers including Abeta42, total tau, P-tau181, neurogranin, neurofilament light chain, and YKL-40. **On 15 May 2020, Cassava Sciences reported that this study missed its primary end points**. However, on 14 September 2020, Cassava Sciences reported that bioassays done by an external group were in error, and that **when patient samples were retested and finalized in what we believe to be Dr. Wang's lab, PTI-125/simufilam was claimed to robustly improve all biomarkers**.



On 26 July 2021, Cassava Sciences presented a poster at the Alzheimer's Association International Conference entitled "SavaDx, a Novel Plasma Biomarker to Detect…" regarding their clinical biomarkers. This poster, featuring Dr. Wang as first author, can be found on their corporate website (https://www.cassavasciences.com/company-presentations | "SavaDx, a Novel Plasma Biomarker to Detect Alzheimer's Disease, Confirms Mechanism of Action of Simufilam"). Figures 4 and 5 of this poster describe effects of 28-day treatment with simufilam (PTI-125) on plasma P-Tau181. Figure 4 shows the percent change from baseline (CFB) and figure 5 shows the absolute biomarker values for individuals before and after treatment. However, Figures 4 and 5 cannot be from the same data set. In Figure 5, one patient in the 100

mg group (at the arrow) had a P-Tau181 level which increased from ~1.5 to 5 pg/ml during the 28-day treatment period, ~235% change from baseline. However, in figure 4 there is no data point in the 100 mg treatment groups showing a CFB >40%. If the correct data point (+235%) were averaged in with the other points in figure 4, any beneficial effect of 100 mg simufilam would likely have been negated.

As a side-note, CSF analysis was also performed on the 13 patients in the phase 2a study and was published by Drs. Wang and Burns in early 2020 in the *Journal of Prevention of Alzheimer's Disease* 7;256-264. Remarkably, this manuscript was accepted for publication Nov. 6, 2020 seven days after submission October 31, 2020. If those dates are correct, it seems highly unlikely to have been subjected to rigorous peer review.

These clinical biomarker data present two significant problems. First, it seems that the primary biomarker data set we have with simufilam in Alzheimer's disease that was entirely produced and finalized by an external lab found that the drug had no effect on clinical biomarkers. Cassava replaced this with a reanalysis that was finalized by an academic lab (presumably Dr. Wang) and showed that simufilam showed remarkable benefit. Second, plasma biomarker data from these same patients, which were just presented by Cassava Sciences, contains evidence of manipulation. If there's no biomarker signal, and there is apparent misrepresentation of clinical data the **continuation of the ongoing Cassava trials may put patients at risk without the claimed evidence of biomarker benefit**. All the clinical biomarker results should be audited and replicated by an independent third party.

C.2. Concern #2: Integrity of Western Blot Data

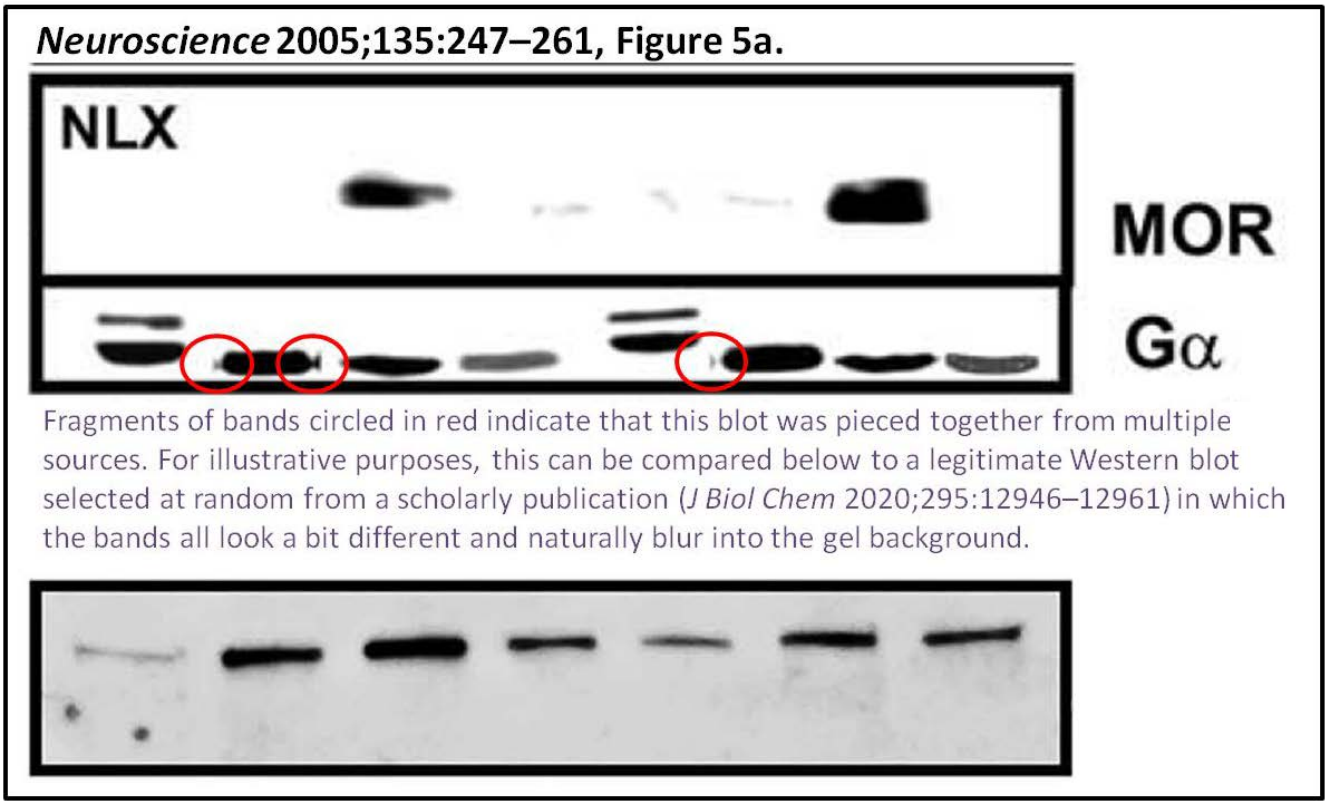
Many experiments in the work by Drs. Wang and Burns involve western blotting. Using this technique, proteins from tissue samples are separated on "gels" in a series of vertical lanes; the proteins are then transferred to a paper-like membrane, and antibodies are used to detect

specific proteins on the membrane, producing an image of specific proteins or "bands".

Each band generally has a slightly different shape. As noted in an article posted on Retraction Watch about data manipulation and focused on Western blots (https://retractionwatch.com/2016/04/19/one-in-25-papers-contains-inappropriately-duplicated-images-screen-finds/), "In Western blots, every band has their own characteristics, they're like faces." That article further noted the significant number of cases of inappropriately duplicated or manipulated Western Blots: "… in no way suggest that Western blotting is a flawed method. Indeed, it suggests that Western blots are harder to fake in an undetectable way than other experimental data." The western blot data presented by Wang and Burns are almost always overexposed and highly processed, which has been repeatedly seen in previously reported examples of image manipulation. In the following sections, we present a series of examples with strong evidence of image manipulation. In the appendix, we include additional examples which raise red flags.

C.2.1. Example #1: Manipulated Western Blot; *Neuroscience* 2005,135:247-261 – Figure 5a.

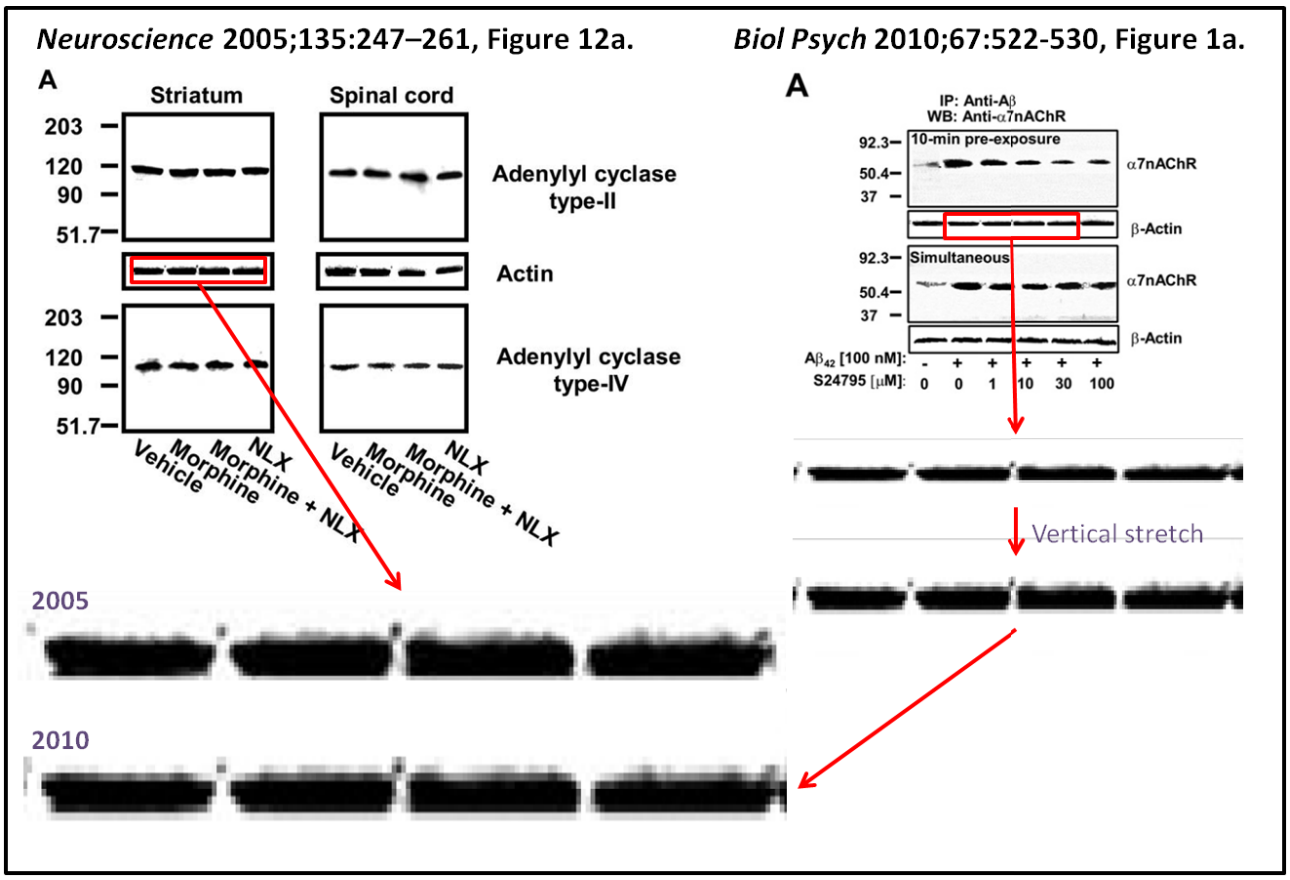
In figure 5a of their 2005 paper *Neuroscience* 135;247–261, the authors appear to have "spliced together" gels from different experiments. Telltale signs that the Gα bands in Figure 5a likely come from different gels are circled in red below. The cropped borders of an adjacent protein band are present indicating the bands were taken from another blot.



C.2.2. Example #2. Falsified Western Blot; *Biol Psych* 2010,67:522 – Figure 1a.

The western blot in Figure 1a (below right) of Dr. Wang's 2010 paper in *Biological Psychiatry* 67:522 contains four bands that closely resemble an image published in Figure 12a (left) of the Wang and Burns 2005 *Neuroscience* 135: 247 paper mentioned in C.2.1. These eight boxed bands come from different experimental conditions that were allegedly conducted many years apart, using different samples. The authors appear to have vertically compressed the bands

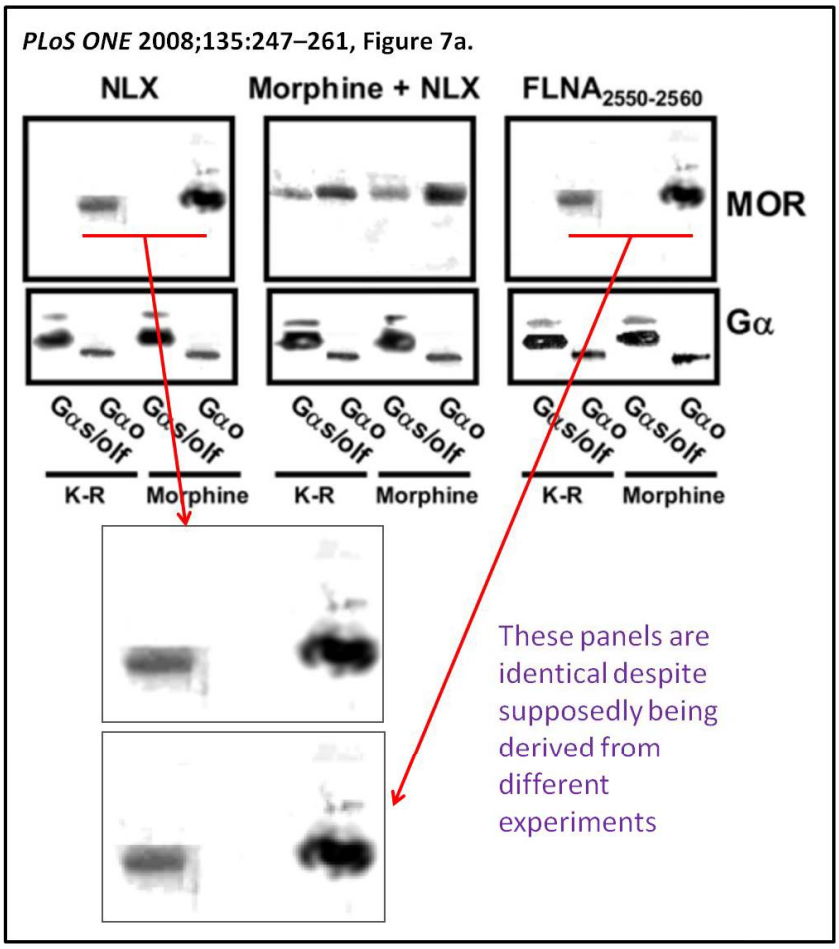
in the 2010 paper, but expanding them here shows they are strikingly similar to those in the 2005 paper. As the sample passes through the gel, it creates a small amount of streaking which causes a distinctive irregular shape in the upper portion of each band; the pattern of this streaking is identical in the two images. This degree of congruence could not have occurred by chance or error; it suggests a complex cross-publication dimension to Cassava Science's band duplication behavior and, in this case, it is hard to imagine that the duplication was not intentional. It is recommended that the original full-length images **with appropriate molecular weight markers are obtained to validate band migration** from both the 2005 and 2010 papers for independent review. Because of the seriousness of this duplication, if the original materials are not available, both of these papers must be retracted.



As a side-note, this western blot was produced on x-ray film, not as a digital image.

C.2.3. Example #3: Reused/Misrepresented Western Blot; *PLoS ONE* 2008;3:e1554 – Figure 7a.

In their 2008 paper *PLoS ONE* 3:e1554, Drs. Wang and Burns again present a series of overexposed and selectively cropped gels that appear to show spliced experiments (i.e., two separate experiments combined as if they were done simultaneously). Suggestive signs include the sharp upper and right border for the band in the Gαo lane (lane 2 from the left in both panels; light blue dashed boxes). Further, Figure 7a of that paper appears to show two IDENTICAL panels (red arrows) for what are reported as different experiments. The similarity in these images could not have occurred by chance. All original full-length gel images **with appropriate molecule weight markers to validate band migration,** from this paper should be requested and analyzed. If they are not available, this paper should be retracted.



C.2.3. Example #4: Band Insertion Into Western Blots. Numerous publications.

The foundational paper from Drs. Wang and Burns that links Filamin A and PTI-125 to Alzheimer's disease is *The Journal of Neuroscience*, 2012 32:9773–9784. This paper appears to contain a collection of questionable western blots. Most of the paper comprises western blots that are of low quality, over exposed and selectively cropped. In this paper, the authors appear to have duplicated and transposed bands. There are dozens of questionable image features in this paper, only a small sampling is presented here. Numerous additional examples of this pattern of behavior in other manuscripts are included in the appendix.

In Figure 1a, the four Filamin A bands in the top set are more similar to each than can be expected by chance and appear to be duplicates. The images at right are magnified, showing that the pixels containing the bands are essentially identical. Additionally, the blots are not aligned and the spacing is irregular. Because FLNA is a large protein (~290kDa), it does not migrate in the gel very far; therefore, this degree of misalignment is suspicious. Moreover, the thin white halos surrounding each band are concerning. There are optical reasons why a halo (or ringing artifact) could occur, but this artifact is most common when components from multiple images are combined using photo editing software. This halo artifact is more prominent in the questionable blots, and extends in some cases into the frame around the blot which is hard to explain as an optical phenomenon.

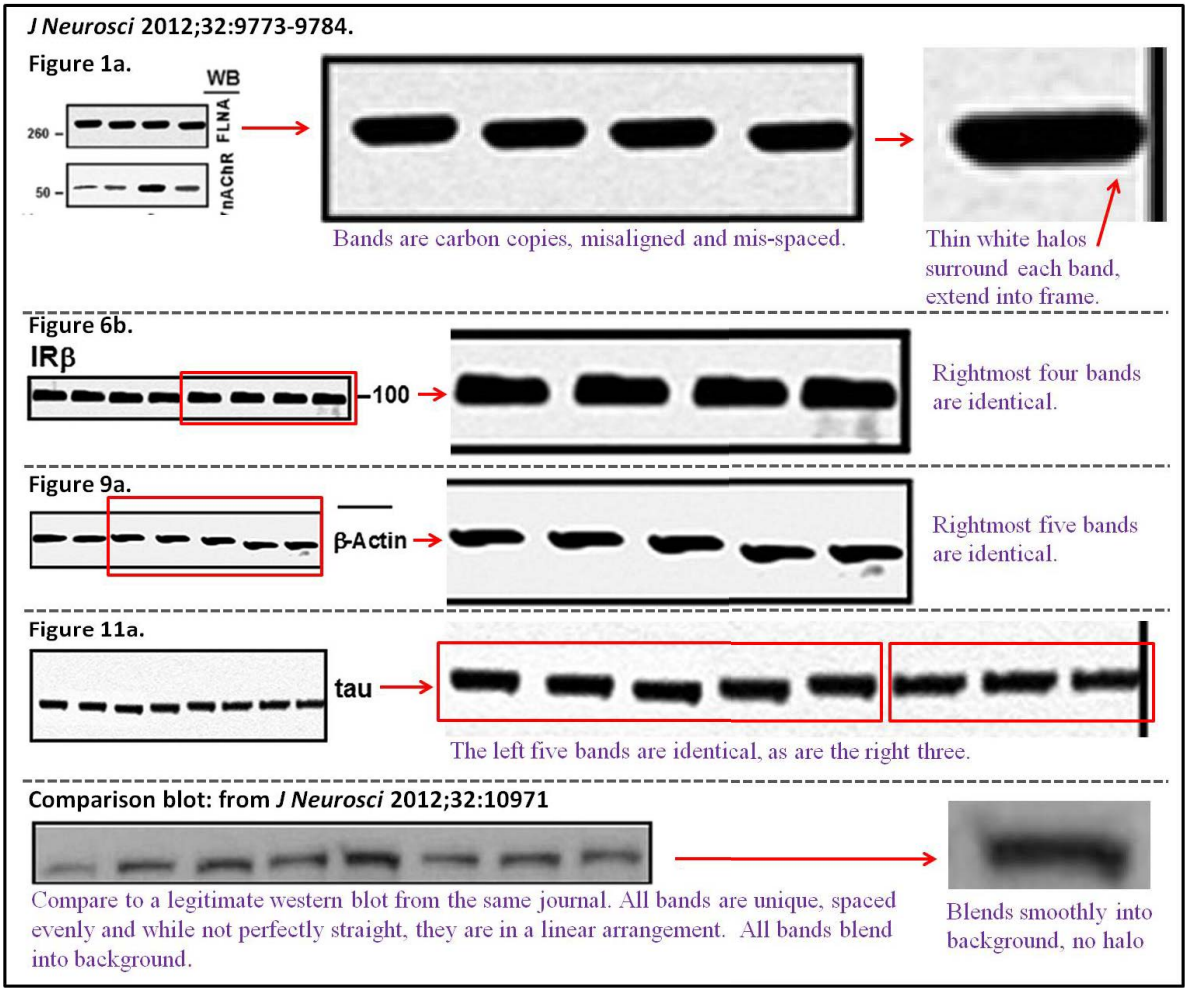


Figure 6b: The four rightmost bands appear to be identical to each other. This degree of similarity is unlikely to occur by chance.

Figure 9a: The five rightmost actin bands have a distinctive shape, but are nevertheless identical to each other. That these bands all have apparently identical "dipper" shapes cannot occur by chance. As above, the thin white border surrounding each band is prominently seen again.

Figure 11a: The five leftmost tau bands appear to be identical to each other, AND the 3 rightmost tau bands appear to be identical to each other. These degrees of similarity are unlikely occur by chance.

There are many other examples that strongly suggest data manipulation in this *Journal of*

Neuroscience paper. Individually, each of these examples is concerning, but together they form a pattern that strongly calls into question the integrity of this publication (and the other publications from these authors with similar patterns of band insertion). The work in question here serves as THE foundational research linking PTI-125 (Simufilam) to Alzheimer's disease. Unless the authors can produce full length unaltered gels with appropriate molecule weight markers to validate band migration, for all experiments in this paper, it should be retracted.

Importantly, data in this paper were part of the package used to garner NIH grant AG060878 and open an FDA investigational new drug application to study PTI-125 (Simufilam) in Alzheimer's disease patients.

C.3. Concern #3: Integrity of Analyses Involving Human Brain Tissue

C.3.1. Implausibility of Reported Pharmacology in Postmortem Human Brain Tissue.

PTI-125/Simufilam is reported to bind to Filamin and alter its conformation. In so doing, it allegedly blocks the interaction between β-amyloid and the α7-nicotinic acetylcholine receptor. This supposedly modifies a range of downstream molecules and signaling pathways including NMDA signaling, Toll-like receptor signaling (causing an anti-inflammatory effect) and decreasing tau phosphorylation.

This is a complex mechanism. In one key line of experiments, the authors report that this entire mechanism can be observed in post-mortem human brain tissue from subjects with Alzheimer's disease and neurological controls. This data is contained in *Neurobiology of Aging* 2017;55:99-114. This builds on similar experiments in *The Journal of Neuroscience* 2009;29:10961-10973 and *The Journal of Neuroscience* 2012;32:9773-9784.

In these experiments, post-mortem human brain tissue is warmed from -80°C to -20°C and chopped into 200micron x 200micron x 3mm blocks with a McIlwain chopper (as a side note, a McIlwain chopper doesn't effectively cut frozen tissue). The resulting chopped tissue is treated with β-amyloid and the experimental drug for 1 hour. They then report a massive increase in tau phosphorylation (modification of the tau protein by enzymatic addition of a phosphate group to the protein; up to 10 fold) from β-amyloid treatment in untreated samples; and that tau phosphorylation was blocked by addition of PTI-125. It is unlikely that the enzyme responsible for phosphorylation would survive the initial -80°C freezing step. Moreover, the phosphorylation experiments are reported to have been performed at 4°C, but it is unlikely that the enzyme responsible for phosphorylation would be active at 4°C (enzymes generally work best at body temperature—37°C).

In a similar experiment, NMDA-receptor signaling was evaluated after incubating minced human brain from patients with AD and neurological controls with NMDA/glycine along with β-amyloid and the experimental drug for 1 hour. NMDA signaling was reported blocked by β-amyloid and in AD and rescued in both cases by the experimental drug. For similar reasons, these reported results are unlikely.

The methodology for the post-mortem human brain experiments among the three studies are virtually word-for-word identical. The age and post-mortem interval for the groups of subjects are the same (down to the decimal points) in each of the three papers. It is therefore reasonable to assume the same human brain specimens were used across the studies from 2008-2017, so the results are premised on the enzymes in the human brain extracts remaining active up to 13 hours post-mortem before freezing, remaining active after nearly 10 years in frozen archival without any advanced cryopreservative techniques, and being active at 4°C.

Importantly, the authors report that there was a marked, rapid increase in the Arc protein observed as evidence of NMDA receptor activity with this approach. The suggestion is that post-mortem human brain tissue, frozen for a decade, thawed and chopped, (1) has intact NMDA receptor signaling, (2) is able to transmit that signal to the cell body through an intact dendrite, (3) has the functioning cellular apparatus to rapidly produce the Arc protein and (4) enough intact neurons are present to mediate a >4 fold rise in Arc levels in this tissue. In reality, neurons in the human brain do not survive extended post-mortem intervals and long-term freezing.

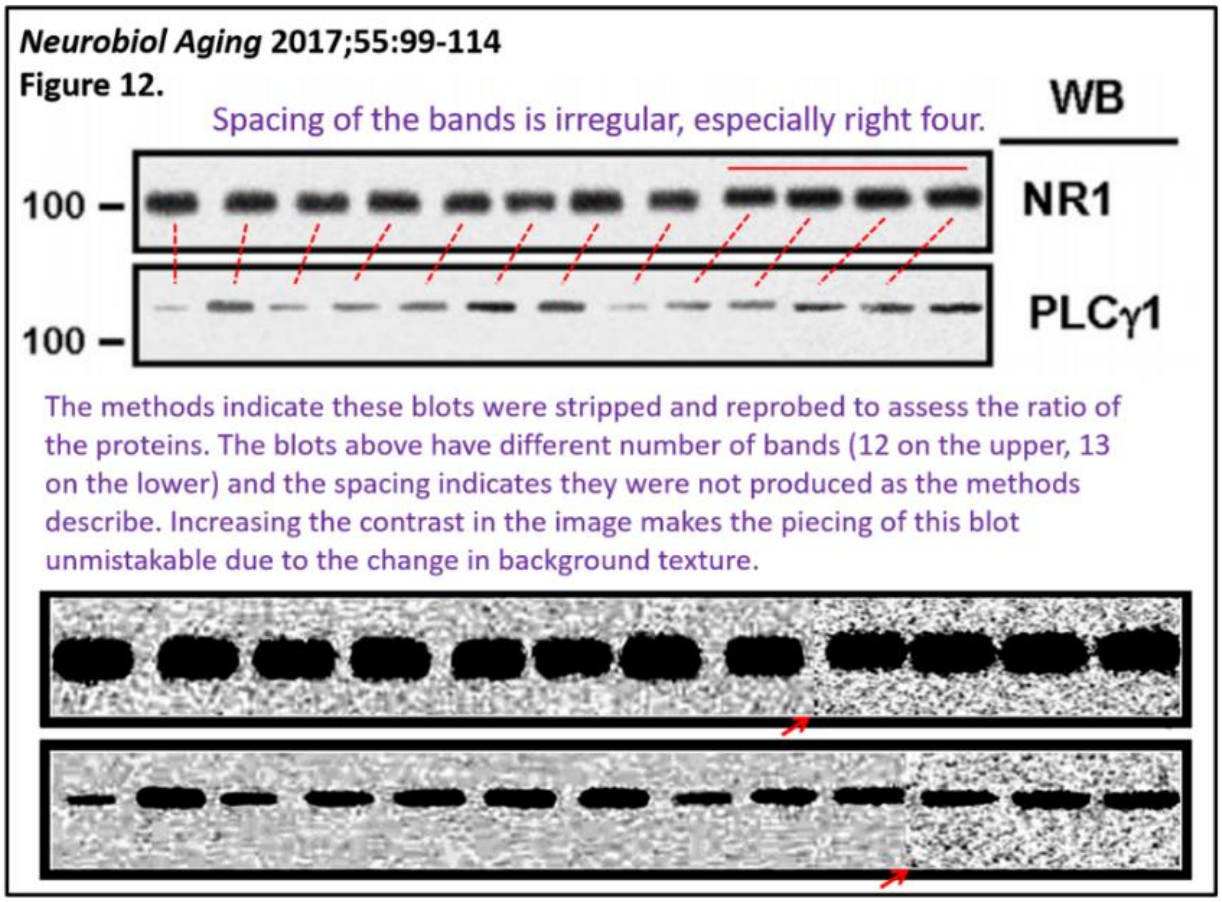
The complex, multi-step cellular processes the authors claim to observe in tissue that has been dead for a decade are contrary to a basic understanding of neurobiology. Claims of this magnitude require extensive, detailed verification, but the authors provide no evidence of tissue

viability. We are not aware of any other research group which has effectively used this technique. As with the western blot data, there are anomalies in the presentation of the data from this human tissue, which again strongly suggest manipulation.

C.3.2. Evidence of Manipulation in Data from Human Tissue

Figure 12 of *Neurobiology of Aging* 2017;55:99-114 uses Western blotting to support their conclusion that PTI-125 improves NMDAR (NR1) function. Their analysis includes a normalization step. In figure 12a (top portion), the NR1 blot that that is used for normalization contains 12 bands whereas all the other blots in this figure contain 13 bands.

Also, the NR1 bands show different spacing than do bands in the PLCγ1 blot, **which strongly suggests that the NR1 and PLCγ1 Western blots could not have derived from the same gel**. This directly conflicts with the author's claim in the method section of this paper that, "Proteins were transferred to nitrocellulose membrane and the levels of PSD-95, and signaling proteins were measured using Western blotting with specific antibodies for PSD-95, nNOS, phospholipase C-γ1, protein kinase C, pY402PyK2, and pY416Src. *Blots were stripped and reprobed with anti-NR1 to assess loading.*" The italicized sentence indicates that the gel membrane was analyzed for PLCγ1, and the same membrane was re-analyzed for NR1. This process does not introduce or remove band lanes.



Another major problem with the 12-band blot is that the spacing of the bands is irregular. This is particularly obvious on the right half (lanes 7-12). This asymmetry in band spacing is incompatible with the regular shape of the combs used for gel loading. Therefore, the 12-band blot was almost certainly pasted together from different sources. Further evidence that the bands likely derive from different sources is apparent when the contrast of the image is adjusted. As shown in the magnified panels in the figure below, in the NR1 (top row) there is a sharp contrast between the background for the leftmost 8 bands and the background for the rightmost 4 bands, marked with a red arrow. In the magnified panel for PLCγ1 (bottom row), there is also evidence of splicing. Again, the red arrow denotes a sharp background contrast between the leftmost 9 bands and the rightmost 3 bands.

For these reasons, the primary data for this paper should be audited. If the primary data

do not support the authors' highly unlikely claims, the paper should be retracted. These questionable experiments used donated cadaveric human tissue, which, if the experimental data are shown to be manipulated, is a particularly egregious ethical transgression.

D. Implications and Recommendations

In summary, it appears that Drs. Wang and Burns in published PubMed indexed manuscripts and through disclosures with Cassava Sciences have misrepresented preclinical and clinical research results for more than 15 years. This initial examination of their published western blots identified many dozens of examples of protein bands that appear to have been duplicated and/or misrepresented, a Western blot that was used twice to represent different experimental conditions, and a normalization blot that appears to have been manually constructed. Some bands appear to have been "reused" in papers concerning different research topics that were published five years apart.

The volume of problematic material uncovered in publicly available sources indicates a thorough audit would likely unveil significant additional scientific misconduct and data manipulation. It is essential that the scientific team behind Cassava Sciences' Simufilam provide the original blots with molecular weight markers to validate these published papers and clinical biomarker data, which include SavaDx.

It is worth repeating, the preclinical and clinical foundations linking Filamin A to Alzheimer's disease derive only from the publications of Drs. Wang and Burns. As shown above, ALL of these papers have evidence of apparent intentional scientific misrepresentation. Cassava Sciences' Alzheimer's disease clinical biomarker data with PTI-125/simufilam showed no evidence of efficacy when tested by an outside lab, and only showed apparent efficacy when re-analyzed in an academic lab—likely Dr. Wang's lab as he is listed as the first author on the

poster (26 July 2021) describing the re-analyzed data. Now, Cassava Science's 26 July 2021 analysis of clinical biomarker results with PTI-125/simufilam also shows evidence of data manipulation.

Finally, the methodology allegedly used to evaluate the function of simufilam in postmortem human brain tissue defies logic and the data presented again have clear hallmarks of manipulation.

In the interests of the NIH, Main Street investors, and most importantly Alzheimer's disease patients, **especially those currently taking simufilam in Cassava Sciences clinical trials**, the issues noted above should be investigated with expediency.

Again, we make six specific recommendations:

- NIH and CUNY should audit the publications and lab of Dr. Wang to determine the existence and extent of data manipulation and fraud in all papers and grant applications from Drs. Wang and Burns.
- The FDA should audit both these publications and the IND application for simufilam's use in AD.
- The FDA should audit all clinical biomarker studies of simufilam in AD.
- The FDA should oversee 3rd party reanalysis of all clinical biomarker studies of simufilam in AD.
- The FDA should pause ongoing clinical trials with simufilam immediately pending these investigations.
- The academic journals which published the studies discussed herein should review the manuscripts and retract them to correcdt the public record, if the concerns remain after adequate investigations.

In particular, there are six papers that require close scrutiny:

- Wang et al. J Prev Alzheimers Dis. 2020;7(4):256-264
- Wang et al. Neurobiol Aging. 2017 Jul;55:99-114
- Wang et al. J Neurosci. 2012 Jul 18;32(29):9773-84
- Wang et al. Biol Psychiatry 2010;67: 522
- Wang, Frankfurt and Burns PLoS One. 2008 Feb 6;3(2):e1554
- Wang et al. Neuroscience. 2005;135(1):247-61

Additionally, the following corporate presentation should be examined:

- (https://www.cassavasciences.com/company-presentations | "SavaDx, a Novel Plasma Biomarker to Detect Alzheimer's Disease, Confirms Mechanism of Action of Simufilam").

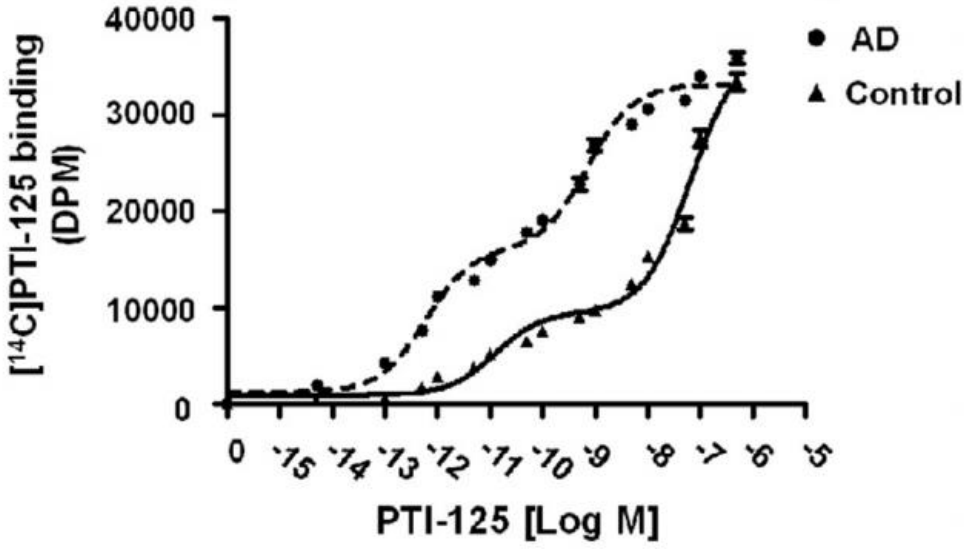
E. Appendix

E.1. Six Additional Areas of Concern

Six further aspects of the research by Drs. Wang and Burns are incompatible with scientific norms, and these claims raise further suspicions. These issues are enumerated below. In addition to the many examples of apparent Western blot manipulation and clinical data misreporting noted above, a number of additional western blots are included at the end of this appendix which raise additional red flags.

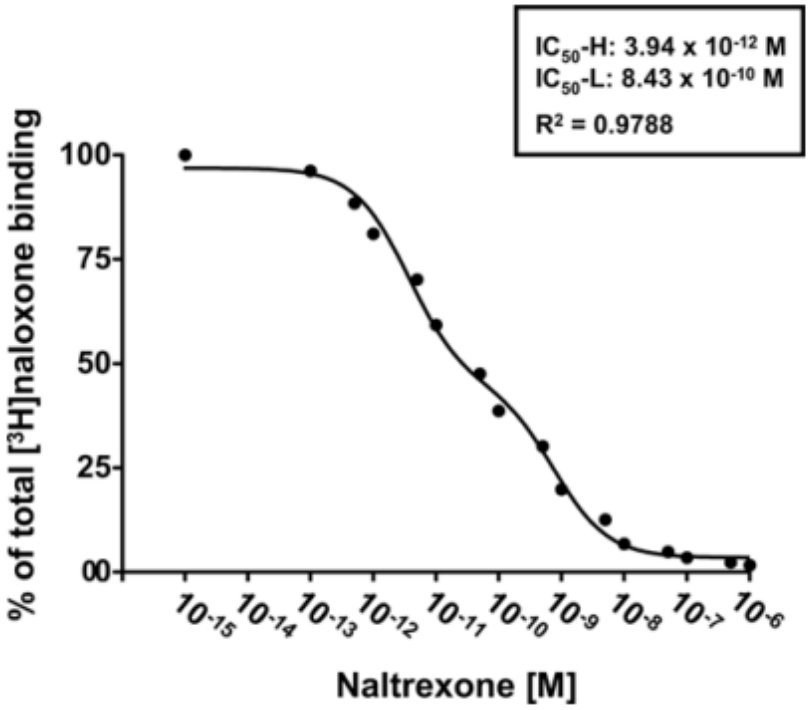
<u>Suspicious Claim #1</u>: Remarkably High Affinity Binding Between PTI-125 and Filamin A

Figure 1B (below) in the *Neurobiology of Aging* 2017;55:99-114 paper claims that PTI-125 has *femtomolar* binding affinity for filamin A in Alzheimer's disease brain. There is scant precedent for a small molecule to bind so potently to a cytoskeletal protein. The claimed affinity seems higher than that of any other small molecule binding to any cytoskeletal protein. Figure 1b in this paper also shows that PTI-125 displacement occurs over 7 orders of magnitude. This "shallow" displacement is highly unusual/unprecedented. An experienced pharmacologist could advise that this is suspicious / implausible. The authors should be asked for the raw data.



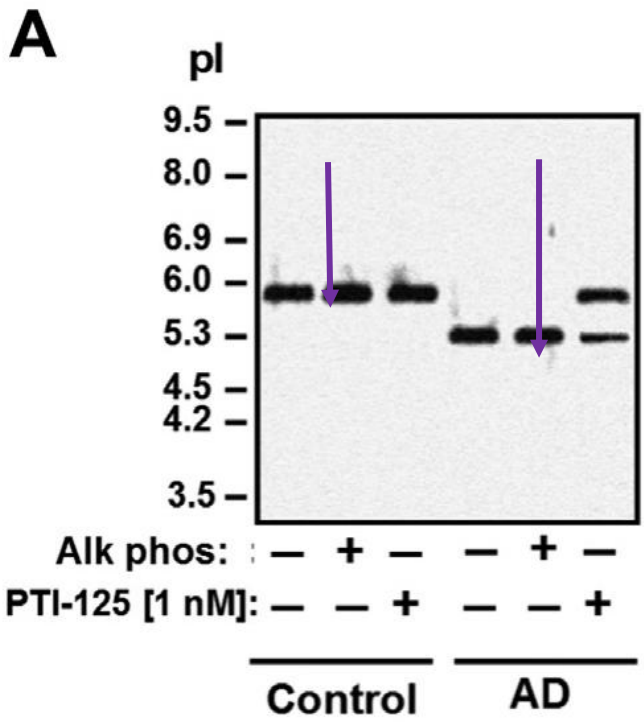
<u>Suspicious Claim #2</u>: Remarkably High Affinity Binding Between Naloxone and Filamin A

Naloxone is an old and intensively studied drug that binds with nanomolar affinity to opiate receptors. Figure 3 (below) of the *PLoS ONE* 2008;3:e1554 paper claims that Naloxone [^{3}H]NLX binds with low *picomolar* affinity to Filamin A. As Filamin A is present in brain, it is puzzling why previous studies have not reported picomolar binding affinity for naloxone in brain. Also unusual is the "shallow" displacement curve in figure 3 that spans 4-5 orders of magnitude. An experienced opiate receptor pharmacologist could advise that this figure is suspicious / implausible. The authors should be asked for the raw data.



<u>Suspicious Claim #3</u>: Isoelectric Focusing Experiments in Multiple Papers Indicate 100% of Filamin in Altered Conformation in Alzheimer's Disease and largely Restored to Correct Conformation by PTI-125

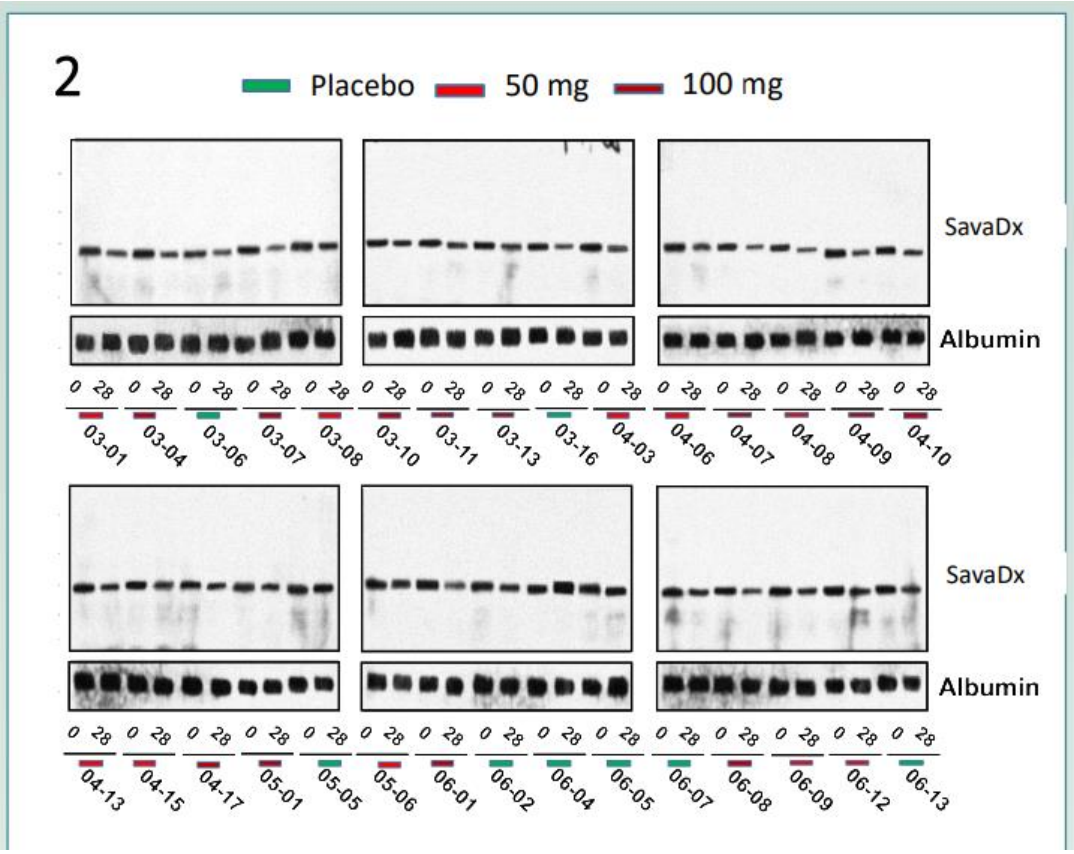
In Figure 2 (below) of the 2017 Neurobiology of Aging 2017 55:99-114 paper, the authors present a gel showing that Filamin A isoelectric point shifts from 5.9 in control to 5.3 in Alzheimer's disease (purple arrows for lanes 1 and 4). This is suspicious for two reasons. First, Alzheimer's disease affects only a small subset of neurons in a diseased brain, so it is scientifically unclear how 100% of Filamin A could shift. Second, isoelectric focusing gels do not typically "look" like the image below. Especially for a 290 kD protein like Filamin A, one would not expect such crisp bands in isoelectric focusing. An experienced biochemist could advise that this figure is suspicious / implausible. This is especially suspect considering the apparent pattern of band manipulation by Drs. Wang and Burns on Western blots. Similar experiments are shown in other publications. The authors should be asked for the raw data.



<u>Suspicious Claim #4</u>: Novel Blood Diagnostic SavaDx Represents Plasma Filamin A Level

Figure 2 (below) in the Cassava Sciences July 26, 2021 poster presentation at AAIC is a collection of Western blots showing that treatment of Alzheimer's disease patients with simufilam lowers their plasma levels of "SavaDx", which the poster defines as "i.e. altered Filamin A levels". Owing to how large (290 kD) proteins run on gels, an experienced biochemist would advise that the blots in figure 2 likely do not represent the 290 kD protein Filamin A. The poster oddly labels the bands as "SAVA Dx" even though they define them as "i.e. altered Filamin A levels".

Considering all of the apparently manipulated western blots in papers from Drs. Wang and Burns, this is particularly suspect. The original blots for this figure should be audited for authenticity.



Suspicious Claim #5: PTI-125/Simufilam Improves Memory in a Mouse Model of Alzheimer's Disease

In *Neurobiol* Aging 2017;55:99-114, figure 9 shows a pre-clinical study of simufilam in a mouse model of AD and misinterprets the data as showing "improvements in memory." It is dubious that any legitimate experiment approximating the methodology described could yield the reported result.

For instance, the third panel (shown below) shows data from a Y-maze which is used to assess memory in mice. Animals are placed in an apparatus made of three tubes which interlock in the middle, like a Mercedes Benz emblem. The test is based on two observations about mouse behavior – (1) when they are put in a new environment, they will explore it and (2) they prefer to explore a new area rather than areas recently explored. After a mouse explores one arm of the y-maze and returns to the center, they must decide which of the other two tubes to enter next. A normal mouse will generally avoid the tube that was most recently explored resulting in a pattern where they spontaneously alternate between each of the tubes. Normal mice would be expected to follow this pattern 70-80% of the time as a rough estimate. If a mouse has memory impairment, the selection of which tube to enter will be random, and the alternation rate should be about 50%. Remarkably, wild type mice and transgenic mice in Wang's study spontaneously alternated less than 20% of the time, which is an atypical result. Drug treatment in 6 month old transgenic mice, increased the rate of alternation to over 30%. This raises a number of issues: (1) this pattern of results is unlikely to occur and suggests, at the least, the experiment was conducted incorrectly, and (2) if the result were legitimate, the drug treatment changing the mice's behavior to closer to 50% spontaneous alternation (i.e., closer to random) would be more accurately interpreted as evidence of *worse* memory performance.

A mouse neurobehavioral specialist would likely advise that there are significant

problems with all of the behavioral and memory data presented in the paper. Importantly, this is the only pre-clinical cognitive/memory data that has been published supporting simufilam's efficacy as a cognitive enhancer. This data should be audited.

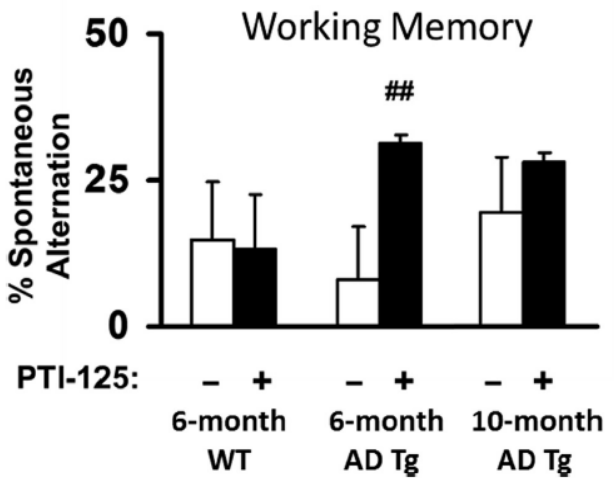
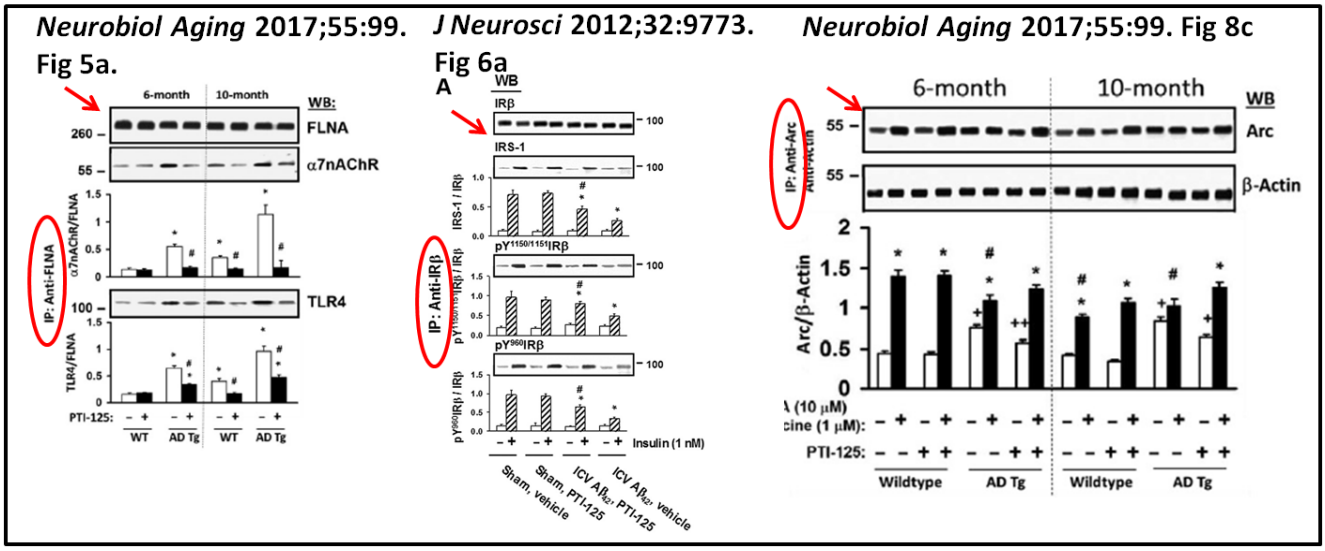


Fig. 9. PTI-125 via drinking water improved nesting behavior in 6-month 3xTg AD mice. Compared to 6-month wildtypes, spatial memory assessed using Y-maze with extra-maze visual cues was impaired in 3xTg AD mice of both ages but not in 3xTg AD mice of either age treated with PTI-125. Additionally, PTI-125 significantly improved spatial memory in 10-month 3xTg AD mice. PTI-125 significantly improved working memory assessed by Y-maze spontaneous alternation paradigm in the 10-month but not 6-month 3xTg AD mice. $n = 5$. $^{*}p < 0.01$, $^{**}p < 0.05$ versus 6-month-old vehicle-treated wild-type group; $^{\#}p < 0.01$, $^{\#\#}p < 0.05$ versus respective vehicle-treated group. Abbreviations: AD, Alzheimer's disease; 3xTg, triple-transgenic.

<u>Suspicious Claim #6</u>: PTI-125/Simufilam Blocks the Interaction Between β-amyloid and α7- Nicotinic Acetylcholine Receptors.

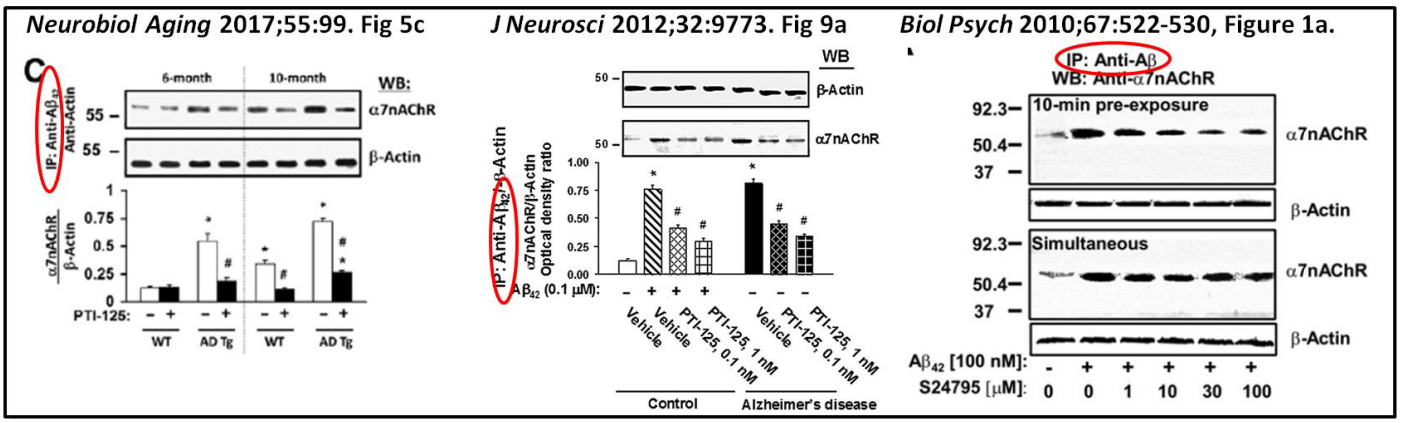
Most of the western blots in these papers take advantage of a process known as co-immunoprecipitation. In this technique, tissue is ground up until it is liquefied and an antibody is used to catch a protein of interest. When the antibody and the protein it binds are isolated, any other proteins that bind to the target protein will also be isolated. This approach enables scientists to evaluate if two proteins interact with each other.

As a standard laboratory practice, the first step in evaluating a co-immunoprecipitation sample is to perform a western blot to confirm that the target protein was captured. It obviously makes little sense to proceed to analyze other proteins, if the target protein was not captured. Drs. Wang and Burns consistently follow this convention. Examples are shown below.

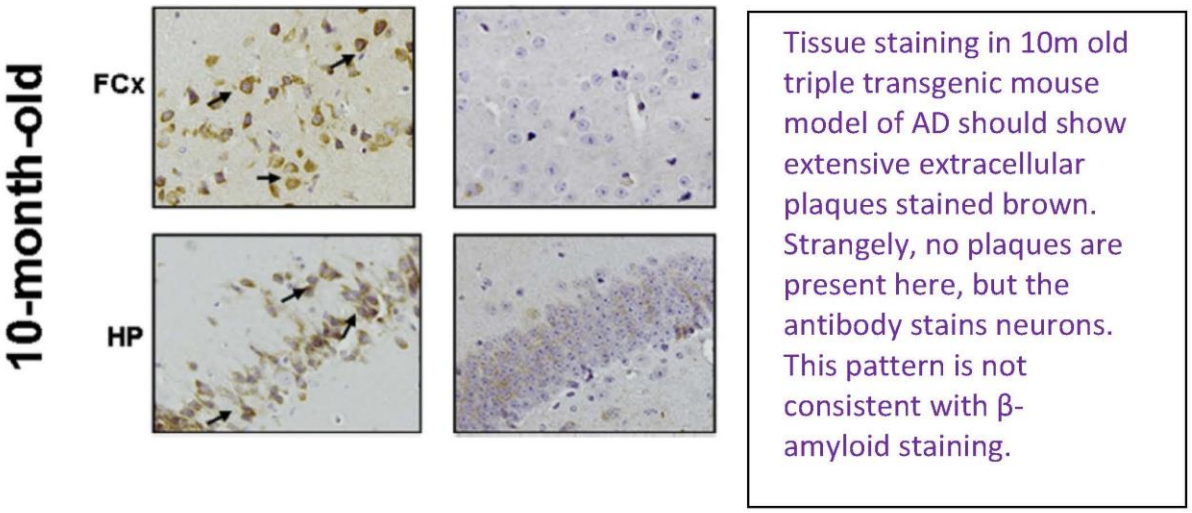


However, there is one exception. The control blot demonstrating efficient capture of the target protein is omitted every time co-immunoprecipitation of β-amyloid is presented. A series of these co-immunoprecipitation experiments is shown below, each omitting this necessary blot. There are numerous other examples throughout the publications. The authors used this technique to build the case that β-amyloid interacts with α7-nicotinic acetylcholine receptors. The fact that

they deviated from a standard of practice they strictly follow in other settings is suspicious. It is also noteworthy that a significant fraction of the western blots shown elsewhere in the document to have been manipulated are associated with β-amyloid co-immunoprecipitation experiments (the center and right example in the figure following also contain two of the more-egregious examples of western blot falsification).



The authors appear to have used the same β-amyloid antibody to perform tissue staining in a transgenic mouse model of AD. Despite the authors' claims, this staining does not show any extracellular β-amyloid plaques (see following figure). It is clear that this antibody is malfunctioning in the tissue staining. Consequently, it is reasonable to be concerned that it is non-functional in the co-immunoprecipitation as well.



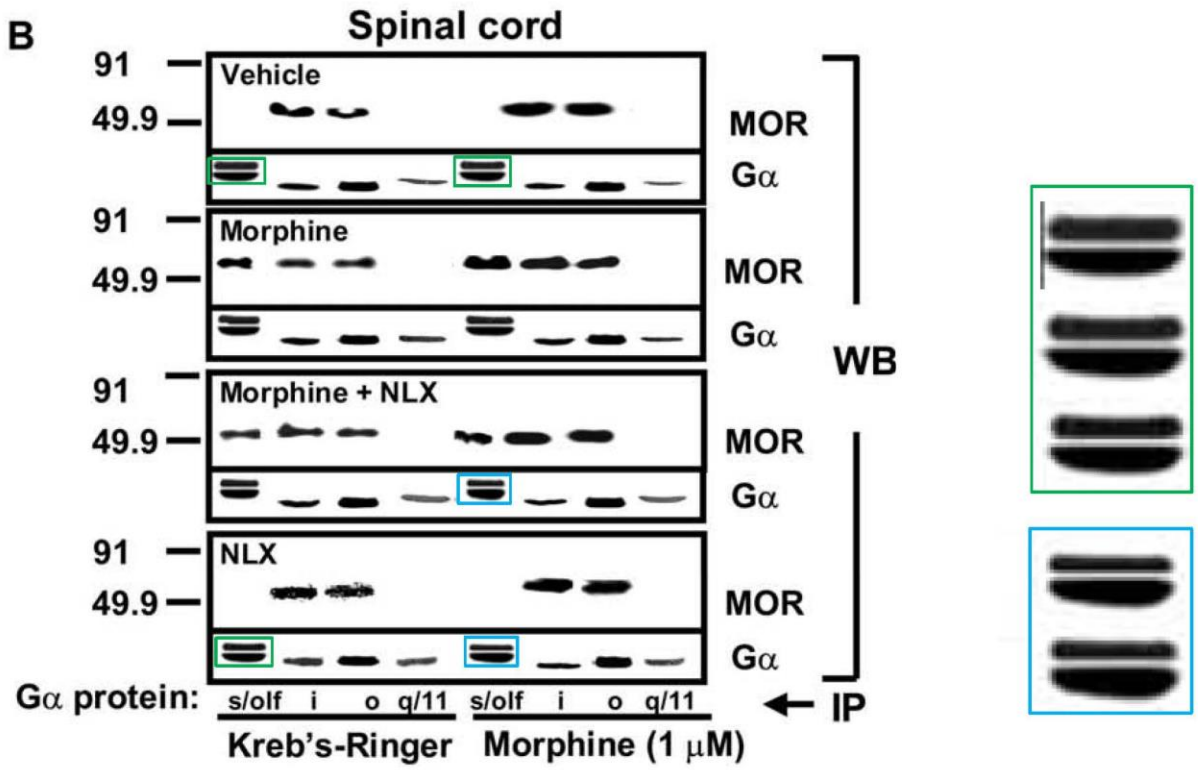
These observations strongly call into question the assertion that PTI-125/simufilam alters the interaction between β-amyloid and any of its supposed targets. The authors should show clear validation of effective immunoprecipitation of β-amyloid in every one of these instances.

E.2. Additional Suspicious Western Blots:

In the 2005 Wang and Burns paper *Neuroscience* 135 247–261, one can see bands with unique features that appear spliced into multiple gels. This suggests that experiments were not conducted as described. One example of this is Figure 5B (below).

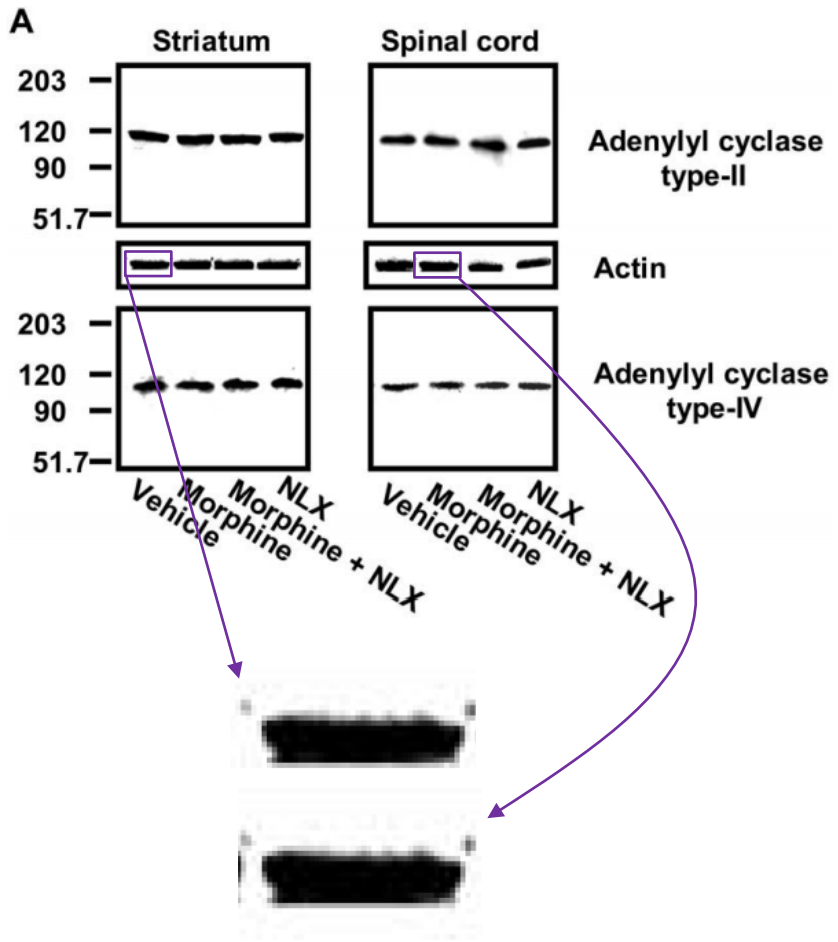
In this Western blot, the Gα bands in the s/olf lanes have peculiar "double decker" shapes. Close inspection reveals that three of these double decker bands (green) are more similar to each other than would be expected AND another two of these double deckers (blue) are also more similar to each other than would be expected.

The congruence of these oddly shaped bands are unlikely to have occurred by chance and raises the possibility of band duplication and data manipulation.



Another striking example of probable band duplication occurs in Figure 12a of this paper. Here, the actin band from the striatum brain region treated with "Vehicle" is indistinguishable

from the actin band from the spinal cord region treated with Morphine. The uncanny resemblance of these "battleship" shaped bands and the precise alignment of the dot artifacts suggest that one or both were intentionally inserted, perhaps with the intention of misrepresenting the results.

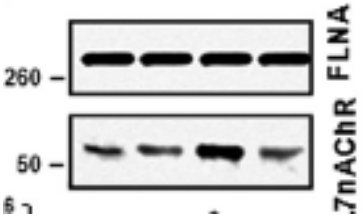


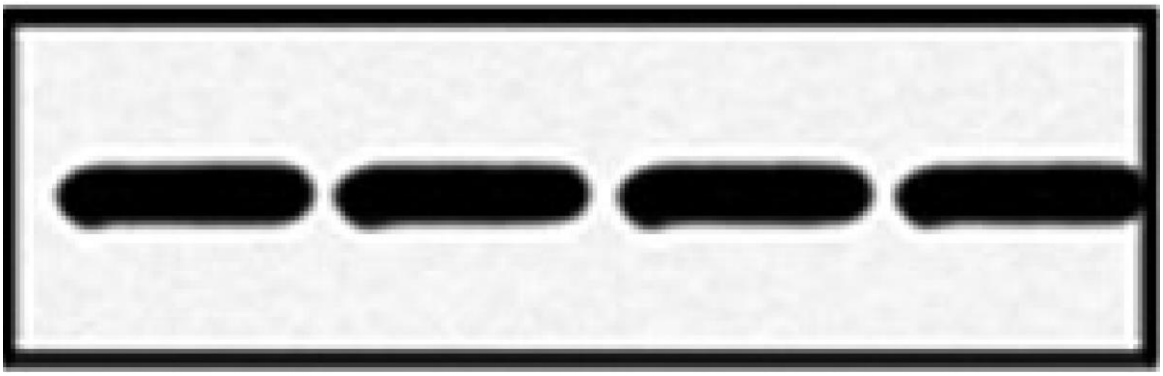
The seemingly identical battleship shape of these protein bands from different

It is recommended that the original full-length images **with appropriate molecule weight markers to validate band migration** from this paper be requested and analyzed. If they are not available, this paper should be retracted.

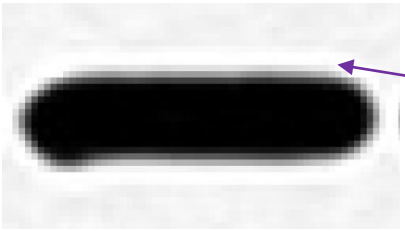
Additional examples of probable band duplication in *J Neurosci* 2012;32:9773-9784.

One can see that the four Filamin A bands in the bottom set of Figure 1A appear to be identical to each other. This degree of similarity is unlikely to occur by chance, and the thin white borders surrounding each band could be due to merging multiple images in a photo editing software.



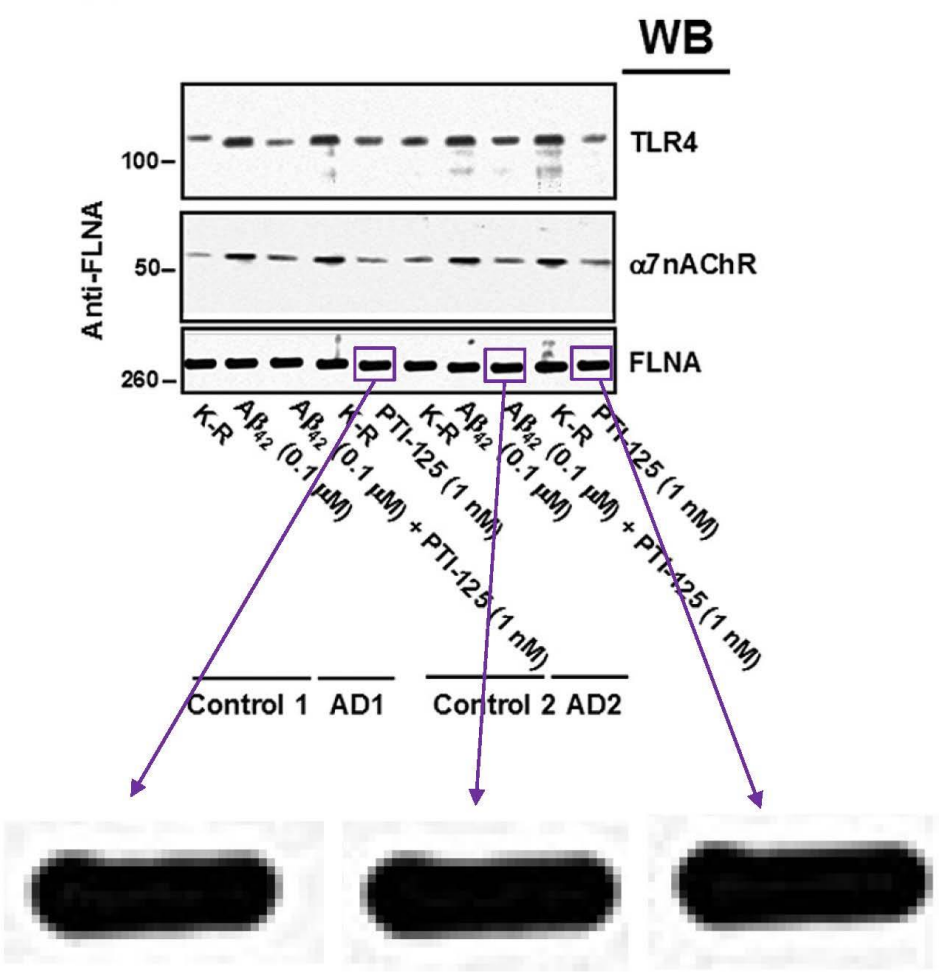


Thin white halos surround each band



Another important consideration is that the Wang and Burns 2012 Journal of Neuroscience paper uses human specimens from Alzheimer's disease patients. Any intentional misuse of such material violates the World Medical Association Declaration of Helsinki regarding ethical use of donated human tissue.

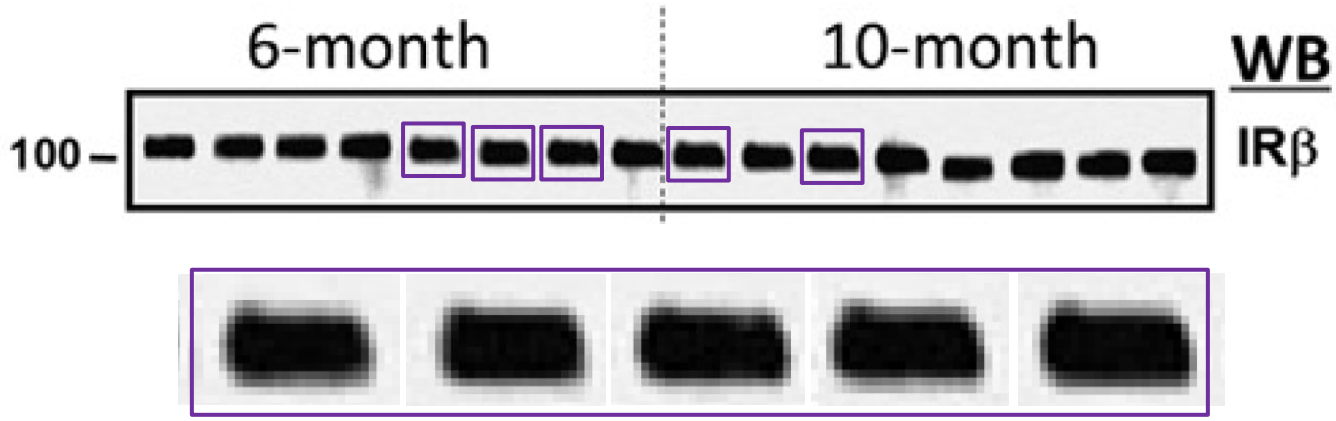
Figure 12A (below) of the Journal of Neuroscience paper, used human Alzheimer's disease tissue to establish the SavaDx biomarker and effects of PTI-125/simufilam. The ten filamin A (FLNA) bands appear identical in size and shape. As protein bands on Western blots typically have unique features, ten consecutive indistinguishable bands are exceedingly unlikely to occur by chance and were probably manually duplicated.



All ten virtually indistinguishable FLNA bands are exactly 11 pixels high and 32 pixels wide. Three examples are magnified here for illustration.

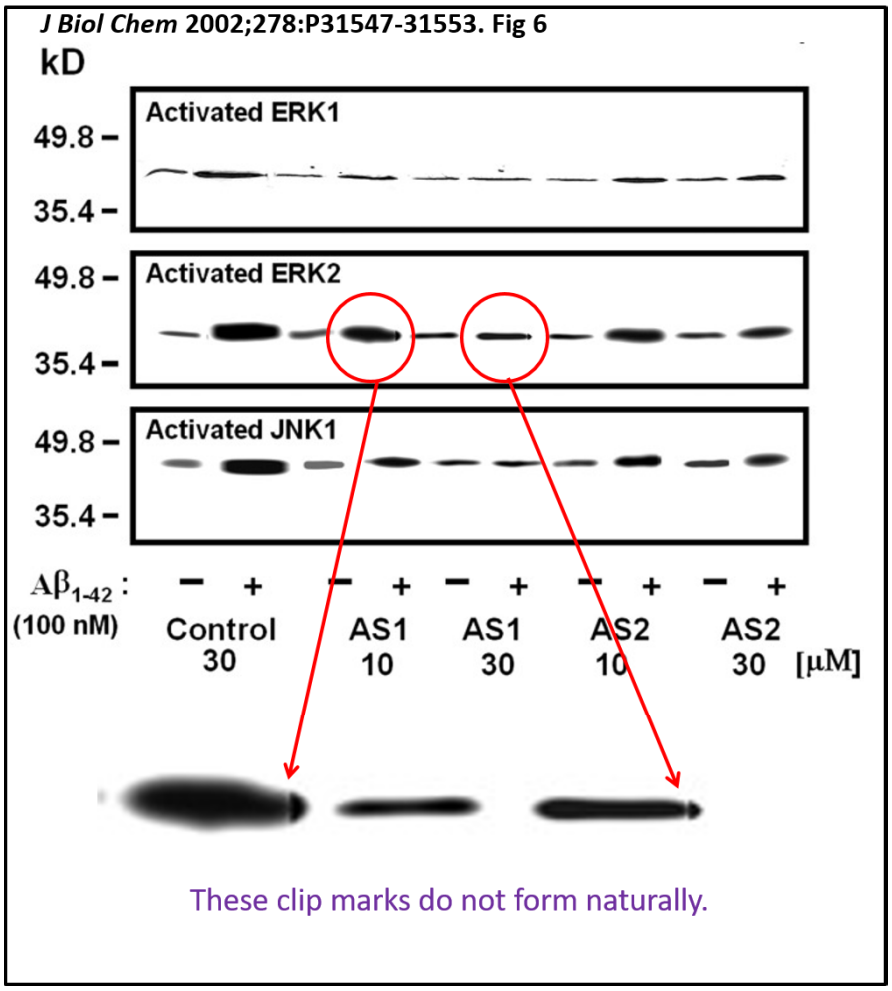
A subsequent paper alleging to connect PTI-125 with Alzheimer's disease is 2017 Neurobiol Aging 55: 99-114. Again, this paper largely comprises a series of overexposed, and apparently manipulated and cropped Western blots. Band duplication appears to occur throughout this paper.

As just one of many examples, Figure 8B contains Western blots from mice treated with PTI-125. The top blot displays a western blot using an antibody for IRβ (see label on the right). The similarity in size and shape of the bands in the purple boxes seemingly could not have occurred by chance. This and many other blots in this paper appear to have been manipulated.



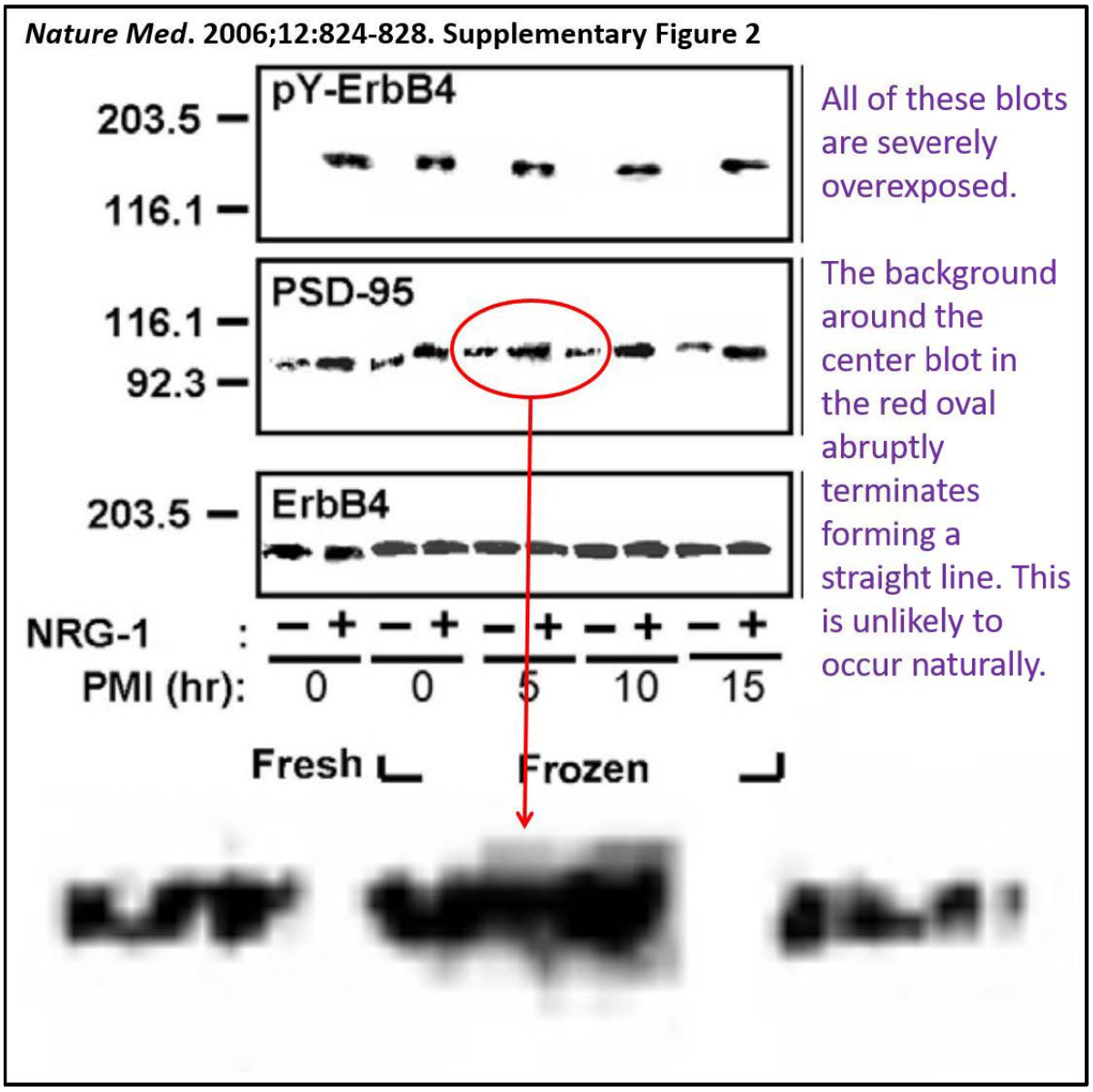
These five indistinguishable bands are all exactly 12 pixels high and 20 pixels wide.

The following example of a manipulated western blot occurred earlier than the examples referenced in the primary document. Dr. Wang was the first author of this 2002 paper in the *Journal of Biological Chemistry* 278:P31547-32553 and it is one of the few examples presented in this document without Dr. Burns as a co-author. The apparent manipulation applied to this blot is similar to that shown in C2.2.1. The marks highlighted at the red arrow do not form naturally and are likely produced by clipping multiple blots together. These blots are also severely overexposed. This study purports to establish that β-amyloid binding to the alpha7 nicotinic acetylcholine receptor induced tau phosphorylation, which is one of the pathways simufilam is supposed to interrupt.

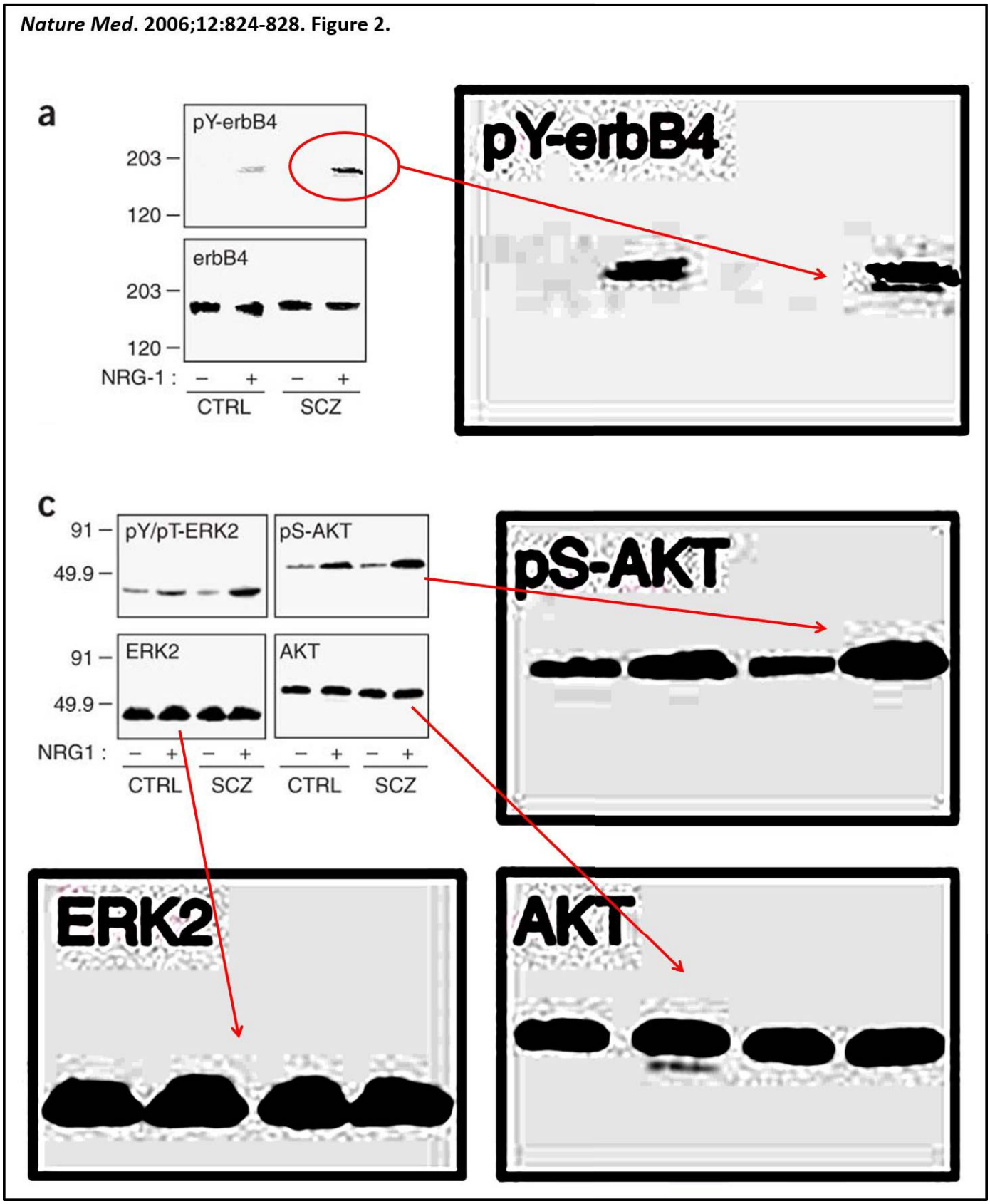


Because of the contemporaneous examples of western blot manipulation, we undertook an evaluation the author's highest profile publication, a 2006 publication in *Nature Medicine* 12:824-828. Dr. Wang is the co-first author of this work. There are numerous suspicious appearing blots in this publication, as well. Again, blots are suspiciously over-exposed. In the supplementary material accompanying that published manuscript, we encounter the blot shown below. The background has more-or-less been obliterated, except for a small area circled in the red oval. Linear termination of the background signal is suspicious for the original blot having been cut and reassembled. Because of the low quality of this image, we evaluated the images in the main manuscript (which are higher quality), to assess for evidence of tampering.

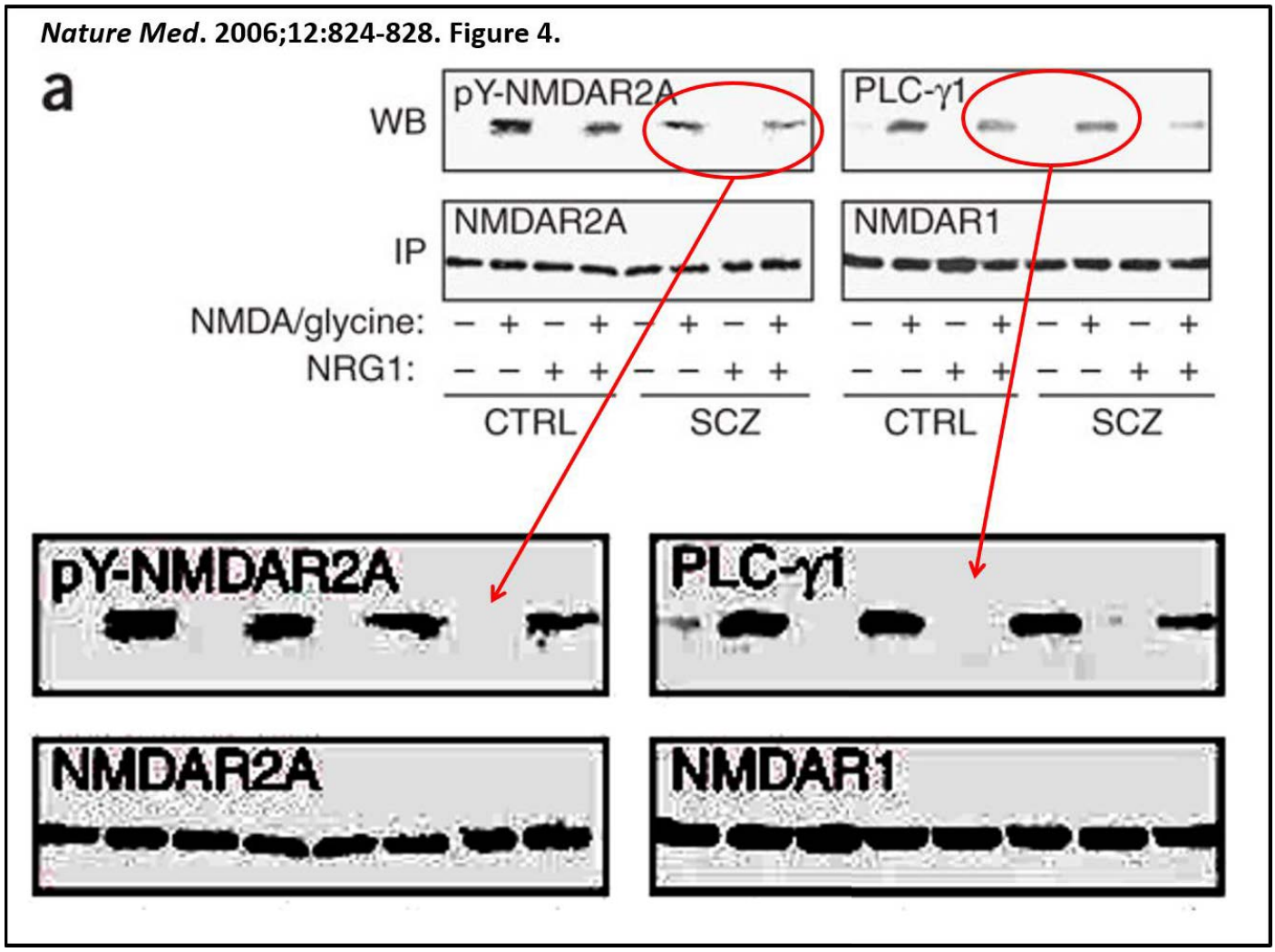
Importantly, this manuscript purports to establish the validity of the functional characterization of NMDA receptor signaling in post-mortem, frozen human brain material which is called into question in section C.3.1. Evidence of tampering with this evidence further calls into question the validity of this unusual technique.


Nature Med. 2006;12:824-828. Supplementary Figure 2
pY-ErbB4
203.5
116.1
PSD-95
116.1
92.3
ErbB4
203.5
NRG-1 : − + − + − + − + − +
PMI (hr): 0 0 5 10 15
Fresh
Frozen
All of these blots are severely overexposed.
The background around the center blot in the red oval abruptly terminates forming a straight line. This is unlikely to occur naturally.

The images in the main text are of higher quality, enabling clearer evaluation. Increasing



the contrast in the images published as Figure 4 (below) clearly reveals evidence of linear cuts in the blots. Importantly, there is clearly a smooth background between the two darker bands and a textured background only behind the dark bands. This was not likely done for cosmetic reasons, it strongly suggests a manufactured/fraudulent result. There is no legitimate explanation for this pattern of findings. This high-profile manuscript should be reviewed by the publisher and retracted. All subsequent manuscripts built on this technique should likewise be reviewed.



DUNN LETTER

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August 18, 2021

VIA FEDEX & EMAIL

Billy Dunn, M.D.
Director, Office of Neuroscience
FDA—Center for Drug Evaluation and Research
10903 New Hampshire Avenue, WO22, Rm. 4212
Silver Spring, MD 20993

Re: *Cassava Sciences, Inc. Whistleblower Submission*

Dear Dr. Dunn:

Cassava Sciences apparently didn't get the Theranos memo. Their desire to do groundbreaking scientific research doesn't give the company and its executives a get out of jail free card from regulators, patients or investors. All stakeholders are entitled to nothing less than the complete truth about what its drug could do today, not what the company hoped it might do someday.

By way of background, Cassava created a drug candidate called Simufilam (previously PTI-125) that they claim binds and stabilizes Filamin A and has beneficial effects in biochemical experiments, animal models, and human brains with Alzheimer's Disease (AD). These studies were used by Cassava to garner NIH grants, to open an investigational new drug application, and to form the basic science foundation for two completed clinical trials, which exposed over 70 patients to Simufilam. Currently, they are recruiting 200 additional patients for a follow-up open label trial. And, according to the company's website, it is planning to start a large (1000 patient, 18 month) phase III AD trial in the Fall.

No other lab has confirmed Cassava's research connecting Filamin A to AD, nor has any other lab confirmed that Simufilam binds or modifies Filamin A or has effects in AD models. This presents a real problem because the company's own research is riddled with red flags. In the accompanying report, we provide extensive details regarding our many concerns about the accuracy and integrity of clinical and preclinical data supporting the ongoing clinical evaluation of Simufilam. The errors and anomalies occur in a pattern that is frequently favorable to Cassava's hypotheses and is of a sufficient frequency and magnitude to strongly suggest scientific misconduct.

Labaton Sucharow

Given the many obvious problems with the underlying research, to protect vulnerable Alzheimer patients, the current clinical trial should be paused while a rigorous audit of Cassava's research is conducted. My clients and the experts we have engaged with are standing by to assist your team with this important work.

Respectfully submitted,

Jordan A. Thomas

Enclosure